The Radioactive Drug Research Committee - Microdosing

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Abstract

Since 1975 the Food and Drug Administration (FDA) has allowed basic clinical research involving radiolabeled drugs at microdose, or sub pharmacologic levels, to be conducted without an FDA Investigational New Drug (IND)application. Although the concept of "microdosing" has only been introduced recently, this program, codified in 21 Code of Federal Regulations (CFR) Part 361.1 established a process by which a medical institution can conduct such research under an FDA approved Radioactive Drug Research Committee (RDRC). The program's intent in 1975 was to encourage basic human research.

Currently there are 83 committees overseeing such research in the United States. RDRC research is considered basic science research. This research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, dosimetry, and localization) of a radioactive drug. It is not intended for therapeutic, diagnostic, or preventive benefit to the research subject, and is not intended to determine the safety and effectiveness of the drug. These type of investigations would require an IND.

RDRC research must be conducted in a facility licensed for the use of radioactive materials in humans and conducted by qualified study investigators. The research protocols must be approved by the associated institutional Review Board (IRB). Research subjects must be properly selected, informed, and any adverse events must be reported to the FDA. Quality assurance testing of the radioactive drugs must be performed, the pharmacologic dose of the radioactive drug to be administered must be low enough to not cause any clinically detectable pharmacologic effect in humans, and specified organ and whole body radiation dose limits must not be exceeded.

Introduction

The Radioactive Drug Research Committee (RDRC) program under 21 CFR 361.1[1] permits basic research of radioactive drugs in humans without an Investigational New Drug Application (IND) when the drug is administered under certain conditions:

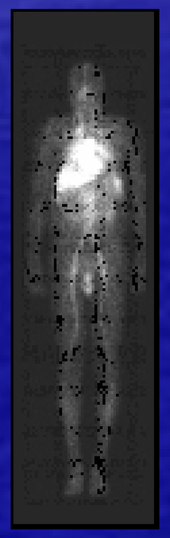
- The research is considered basic science research and is done for the purpose of advancing scientific knowledge. This type of research is:
  - intended to obtain basic information regarding the metabolism (including kinetics, distribution, dosimetry, and localization) of a radioactive drug or regarding human physiology, pathophysiology, or biochemistry,
  - not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject from the research, and
  - not intended to determine the safety and effectiveness of a radioactive drug in humans as a therapy, diagnostic, or preventive medical product.
- The research is generally recognized as safe if the following criteria are met:
  - The pharmacologic dose of the radioactive drug to be administered is not known to cause any clinically detectable pharmacologic effect in humans.
  - The radiation dose to be administered is within the limits specified in 21 CFR 361.1(b)(3).
- The research study is approved by an FDA-approved RDRC based on the following requirements:
  - qualified study investigators
  - properly licensed medical facility to possess and use radioactive materials
  - appropriate selection and consent of research subjects
  - appropriate quality assurance of radioactive drug administered
  - sound research protocol design
  - reporting of adverse events by the investigator to the RDRC
  - approval by an appropriate Institutional Review Board (IRB)

Microdosing, Imaging, and FDA's Critical Path Initiative

The term “microdosing”[2] has recently been used to describe the use of very small doses of a drug, considered to be safe, and used in humans to obtain basic biodistribution information. This has the potential of reducing the number of preclinical (animal) studies essential for conducting early clinical (human) studies, differentiating between good and bad candidate drugs early, and speeding up the early phases of drug development.

FDA's Critical Path Initiative also relies on imaging to obtain basic biodistribution data in drug development.

FDA's RDRC program has been allowing such research since 1975, with certain restrictions. Research is not allowed on new molecular entities (NME's), there must be “no clinically detectable pharmacologic effect”, what is now referred to as microdosing, and radiation doses to the whole body and specific organs may not exceed certain limits.



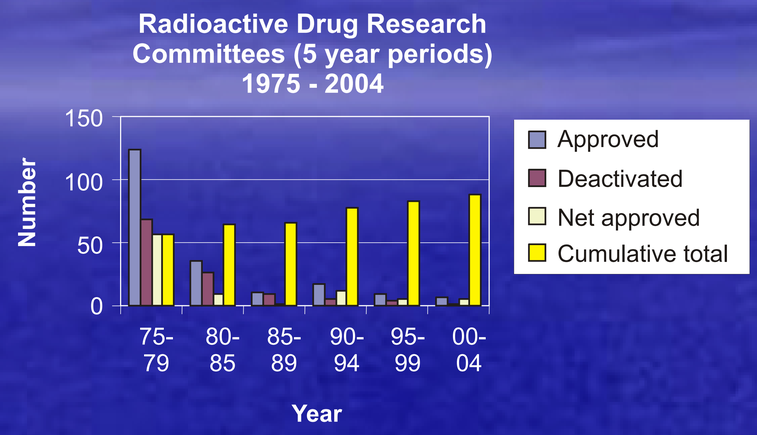
Radiation Dose Limits for RDRC Subjects

For adult subjects: Radiation dose from a single study or cumulatively from a number of studies conducted within 1 year does not exceed:

Limits of Radiation Dose for Adults		
Organ or System	Single Dose	Total Annual Dose
Whole body	0.03 Sv (3 Rem)	0.05 Sv (5 Rem)
Active blood-forming organs	0.03 Sv (3 Rem)	0.05 Sv (5 Rem)
Lens of the eye	0.03 Sv (3 Rem)	0.05 Sv (5 Rem)
Gonads	0.03 Sv (3 Rem)	0.05 Sv (5 Rem)
Other organs	0.05 Sv (5 Rem)	0.15 Sv (15 Rem)

For subjects under 18 years of age: Radiation dose does not exceed 10 percent of dose set forth above.

RDRC Research Since 1975



RDRC Research in 2002

RDRC Radionuclides
In 2002, 83 FDA approved RDRC's conducted 280 studies with 2872 human subjects

Imaging nuclides		Non-imaging nuclides
positron	gamma	beta
C-11 (32%)	Tc-99m (2%)	H-3 (15%)
O-15 (20%)	I-123 (1%)	C-14 (6%)
F-18 (18%)		
N-13 (2%)		
Other nuclides (4%): Cu-60, Fe-59, Ca-41, F-17, Fe-55, I-25, I-131, Ca-45, Ca-47, Cu-62, In-111, Tc-94m, Xe-133		

Discussion

Elements of new initiatives to improve human research on drug development, such as FDA's Critical Path Initiative and Microdosing, can be seen in FDA's RDRC program. This program relies on a local committee of qualified experts to provide the necessary oversight to conduct such basic human research safely.

References

1 Title 21 Code of Federal Regulations Part 361.1 Prescription Drugs for Human Use Generally Recognized as Safe and Effective and Not Misbranded:Drugs Used in Research. Radioactive Drugs for certain research uses.

2 Lappin G and RC Garner. Big Physics, small Doses:the use of AMS and PET in human microdosing of development drugs. *Nature Vol 2: 233 240, March, 2003 233 -240.*